UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/755,734	01/04/01	PODSAKOFF G	0800-0009.05

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HM22/0830

EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 08/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/755,734	Applicant(s) PODSAKOFF ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 23-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23, 25- 29, and 31-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 6,211,163 (4/3/01), hereafter referred to as Podsakoff et al. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons: the patented claims represent a species of the broader instant claims. The patented claims of Podsakoff et al. are drawn to methods of administering recombinant adeno-associated virus virions encoding a gene into the bloodstream of a mammalian subject comprising delivering the virions by intravenous injection. The instant claims are broader in that they are not limited to intravenous injection. However, it is noted that the specification clearly discloses the use of intravenous

injection to introduce the recombinant AAV virions into the bloodstream, see specification page 40). Thus, the species of the patented claims renders the genus of the instant claims obvious.

Specification

Claims 24 and 30, added by pre-amendment with the filing of the continuation application, are objected to because of the following informalities: claims 24 and 30 recite the word "intraarterially" which is not disclosed anywhere in the instant specification. The specification is also objected to as failing to provide proper antecedent basis for the claimed subject matter of claims 24 and 30, specifically the recitation of delivery of rAAV "intraarterially". See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The applicant's specification discloses methods of administering recombinant adeno-associated virus virions (rAAV) into the bloodstream of a mammalian subject and methods of expressing a therapeutically effective amount of a protein in a mammalian subject comprising delivering an rAAV to the bloodstream, whereby a genes encoded by the rAAV is expressed at a level which provides a therapeutic effect in the mammalian subject. Specifically, the specification discloses that in preferred embodiments of the invention the therapeutic protein is useful for treating a blood disorder, such as hemophilia, and the delivery to the bloodstream is by intravenous or intraarterial administration of the rAAV. It is noted that the specification discloses the purpose of delivering and expressing therapeutic levels of protein using the rAAV of the instant invention is the treatment of diseases, specifically blood disorders.

The specification provides a single working example of the instant invention of delivery of rAAV to the bloodstream which demonstrates that the intravenous injection of rAAV-hEPO which expresses hEPO using the CMV promoter in mice results in detectable levels of circulating hEPO. However, it is noted that the level of hEPO observed following intramuscular injection was 60 fold higher than that observed with intravenous injection. However, the applicant's have also included in the information disclosure statement (IDS) received on 2/5/01 several post-filing publications co-authored by the instant inventors. The Kessler et al. reference, BM-1, discloses in greater detail the data found in the applicant's working examples 4 and 5 which demonstrate that both intramuscular and intravenous injection of mice with rAAV-hEPO which expresses hEPO

using the CMV promoter results in detectable levels of circulating hEPO and a corresponding increase in hematocrit levels. It is noted however, that similar to the working examples, the reference demonstrates that intramuscular injection of rAAV-hEPO results in substantially higher levels of circulating hEPO than intravenous administration and that authors fail to correlate the level of hEPO expression and the observed increases in hematocrit level using either mode of administration with any therapeutic effect on any blood disorder. The Watson et al. reference, CL-1, discloses the intravenous administration of an rAAV encoding β-glucuronidase (GUS) under control of the CMV promoter in mice with MPS, a lysosomal storage disease, resulting in the expression of GUS in liver, heart, and muscles but not in other tissues. Watson et al. further discloses that in the liver, where GUS was expressed at low but detectable levels, storage vacuoles were reduced, whereas in kidney and brain, which did not express GUS, storage granules persisted. However, as the paper notes, lysosomal storage syndromes affect every cell in the body, and the expression of GUS in one or two organs is insufficient to treat the disease. The Brockstedt et al. reference, AT-1, discloses the intravenous administration of rAAV encoding OVA under control of the CMV promoter. Brockstedt et al. demonstrates that intravenous injection of rAAV-OVA results in the generation of OVA specific CTL and antibodies similar to that obtained using intraperitoneal injection which the authors show is sufficient to reduce the growth of an OVA expressing tumor in mice. However, the skilled artisan would not consider the challenge of mice with an OVA expressing tumor as a model for cancer as ovalbumin is a highly immunogenic protein that is not a naturally occurring tumor antigen. Finally, the Nakai et al.

publication, BX-1, discloses rAAV encoding human factor IX under control of either the CMV or the EF1α promoter, and demonstrates that intravenous injection of rAAV-F.IX -EF1α into the portal vein of normal mice results in expression of Factor IX in mouse liver and concentrations of Factor IX in the serum which correspond to therapeutically effect levels in humans with hemophilia. It is noted that the rAAV-F.IX.-CMV virus failed to express detectable levels of Factor IX in adult mice following portal vein injection.

The specification does not provide an enabling disclosure for achieving therapeutic levels of expression of any protein capable of treating any disease or condition by administration of an rAAV which utilizes any promoter to express the therapeutic gene of interest by any method of delivery to the bloodstream. It is noted that neither the art at the time of filing nor the specification provides guidance for methods of rAAV delivery to the bloodstream other than intravenous injection. The specification reads broadly on the treatment of any and all diseases using both membrane bound and secreted proteins. The specification does not provide sufficient guidance for achieving therapeutic levels of gene expression in any and all tissues or disclose what level of gene expression correlates with any therapeutic effect. Further, some diseases may require direct expression of a therapeutic gene in the cell itself whereas other may benefit from systemic or local therapeutic protein exposure. The Watson et al. reference, discussed above, demonstrates that intravenous injection of a particular rAAV encoding GUS resulted in the expression of GUS in a limited number of tissues such as liver, heart, and muscle, and not in other tissues such as kidney and brain. Thus, in view of the teachings of Watson et al., the skilled artisan would not

have predicted that intravenous injection of rAAV would be capable of generating therapeutic gene expression in kidney or brain tissue of patients with kidney disease or neurological disorders, or of treating somatic disorders which affect every cell type. Further, the specification does not provide sufficient guidance as to the identity of promoters capable of producing therapeutic levels of gene expression in any and all types of cells. Comparison of the Watson et al. and Nakai et al. references discussed above demonstrates the unpredictability of achieving gene expression in a particular type of cell using the same promoter to drive the expression of different genes of interest. Whereas Watson et al. observed GUS gene expression in liver cells infected with rAAV encoding GUS operatively linked to a CMV promoter following intravenous rAAV injection, Nakai et al. failed to observe expression of Factor IX in liver cells following intravenous injection of a similar rAAV encoding Factor IX operatively linked to CMV.

Furthermore, at the time of filing, the art teaches that *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of viral vectors or plasmid vectors was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and

page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, "the search for such combinations is a case of trail and error for a given cell type" (Verma, (1997) Nature, 389, page 240).

In addition, cancer immunotherapy using tumor antigens is further complicated by the fact that in order for the tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen. At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteosome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent from being recognized by the tumor specific cytotoxic T cells.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression in any and all cells using viral vectors encoding any therapeutic gene and any promoter, the limited tissue expression of genes encoded by adeno-associated viruses following intravenous injection, the lack of correlation between the combined teachings of the applicant's working examples and the post-filing references provided with the applicant's declaration and the treatment of any and all diseases, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of protein to any and all types of cells via intravenous injection of rAAV, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

The claims are free of the prior art of record, as the prior art does not teach or suggest methods of achieving therapeutic levels of gene expression in mammals by directly administering recombinant adeno-associated virus encoding a gene of interest to the bloodstream of a mammal.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should

be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER